

**Remarks Regarding New Claims:**

Amendments to Claims 1, 4 and 5 are for purposes of conforming the claims to the elected species only and are supported by pages 15 and 19 of the specification.

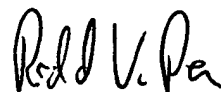
**RESPONSE**

***Election/Restriction***

The Applicants elect Group I, with Example 1 as a species--wherein A is a five-membered monocyclic heterocyclic ring consisting of one ring nitrogen and V is a carbocyclic radical--with traverse.

Applicants respectfully submit that no serious burden is imposed upon the Examiner by not restricting the claims, because the Examiner has not shown how a search of Groups I and II would be any more burdensome than a search of Group I alone. Therefore, Applicants respectfully request that the restriction requirement be withdrawn.

Respectfully submitted,



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Date: February 22, 2002

Please send all future correspondence to:

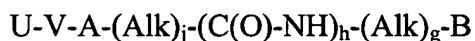
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Dept. 4300, M/S 27-4-A  
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Thousand Oaks, California 91320-1799

Marked-up changes:

Page 3, first full paragraph:

Integrin  $\alpha_5\beta_1$  is an RGD, tenascin and fibronectin binding protein (J. Biol. Chem. 267:5790-6, 1992) which is expressed by a number of cells, such as carcinoma and epithelial cells, and is thought to be involved in carcinoma cell proliferation (J. ~~Biol. Chem.~~ Cell Biol. 127:547-56, 1994), in wound healing and cell attachment (J. Invest. Dermatol. 106:42-8, 1996), in epithelial inflammation, such as asthma (J. Cell Biol. 133:921-928, 1996), in inducing gelatinase B secretion, activation of the protein kinase-C pathway, tumor cell spreading and proliferation in colon cancer cells (Biochem. Biophys. Res. Commun. 249:287-291, 1998; Int. J. Cancer 81:90-97, 1999), in regulation of pulmonary inflammation and fibrosis and binding and activating transforming growth factor  $\beta_1$  (Munger et al., Cell (Cambridge, Mass) 96:319-328, 1999), and in viral infections (Virology 239:71-77, 1997).

1. (Amended) A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein g, h and j are each independently 0 or 1; provided when h is 0, then g is 0;

each Alk is independently a alkyl radical;

U represents amidino, guanidino,  $-(G-alkyl)_k-NH-R_1$ ,  $-(G-alkyl)_k-NH-C(Q)-R_1$ ,  $-(G-alkyl)_k-C(Q)-N(R)-R_1$ ,  $-(G-alkyl)_k-NH-C(Q)-N(R)-R_1$ ,  $-(G-alkyl)_k-NH-C(Q)-O-R_1$  or  $-(G-alkyl)_k-O-C(Q)-N(R)-R_1$  radical; or U represents a hydroxyalkyl-G- radical which is optionally substituted by a cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of  $R_2$ ;

wherein k is 0 or 1;

G represents a bond, O, S or NH;

Q represents O, S, NH, N-CN or N-alkyl;

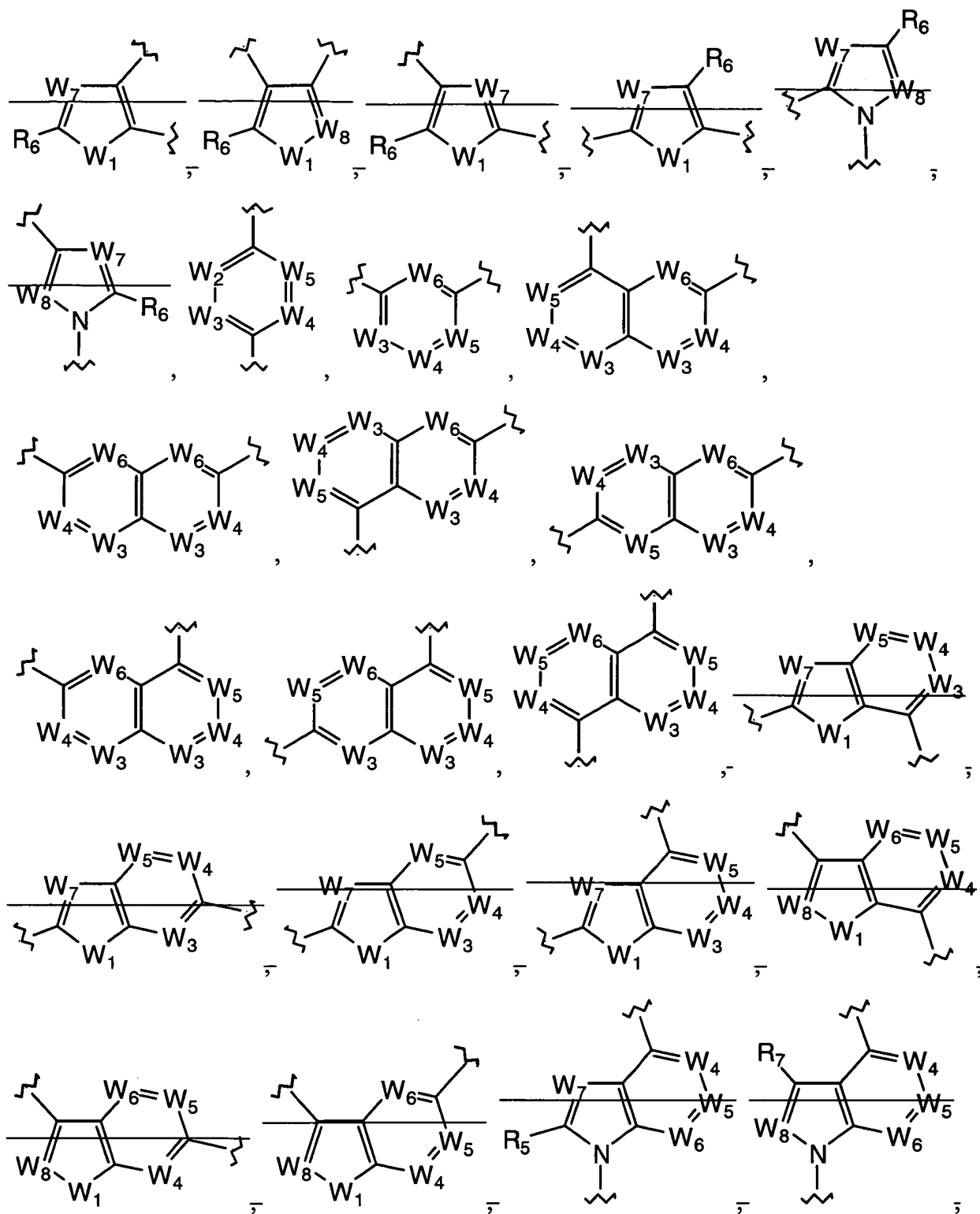
R is a radical of hydrogen or alkyl;

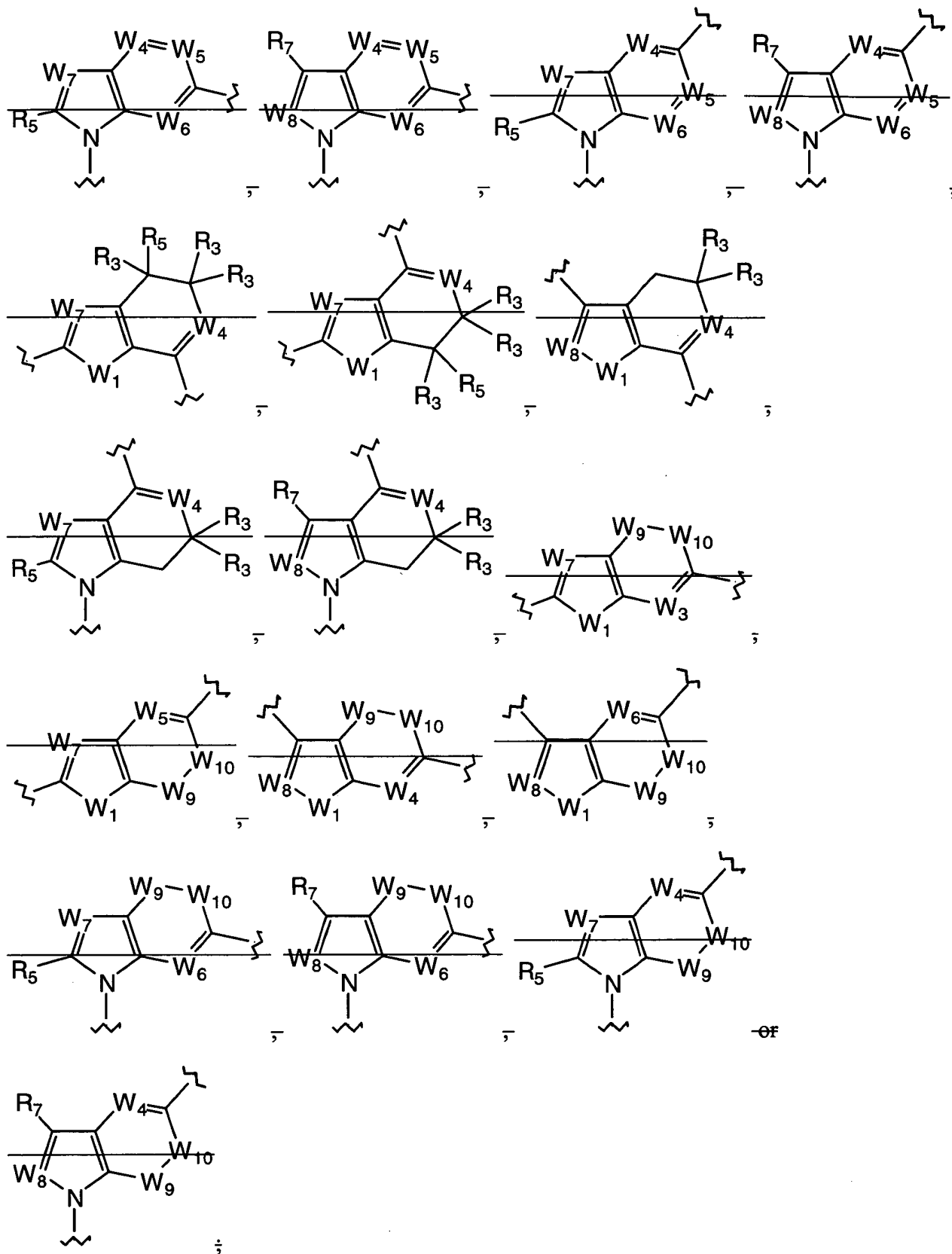
R<sub>1</sub> is a radical of alkyl, haloalkyl, R<sub>21</sub>R<sub>22</sub>N-alkyl, R<sub>21</sub>O-alkyl, R<sub>21</sub>S-alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R<sub>2</sub>;

wherein R<sub>21</sub> and R<sub>22</sub> are each independently a radical of hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R<sub>2</sub>;

each R<sub>2</sub> is independently a halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, alkylamino or dialkylamino radical or two adjacent R<sub>2</sub> radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

V represents a radical of formula





wherein  $W_1$  is O, S or N- $R_3$ ; wherein each  $R_3$  is independently a hydrogen or alkyl radical;  $W_7$  is N or C- $R_7$ ;  $W_8$  is N or C- $R_5$ ;

~~$W_9$  is  $C(R_3)_2$  and  $W_{10}$  is  $W_4$ ; or  $W_9$  is C- $R_3R_5$  and  $W_{10}$  is  $C(R_3)_2$ ;~~

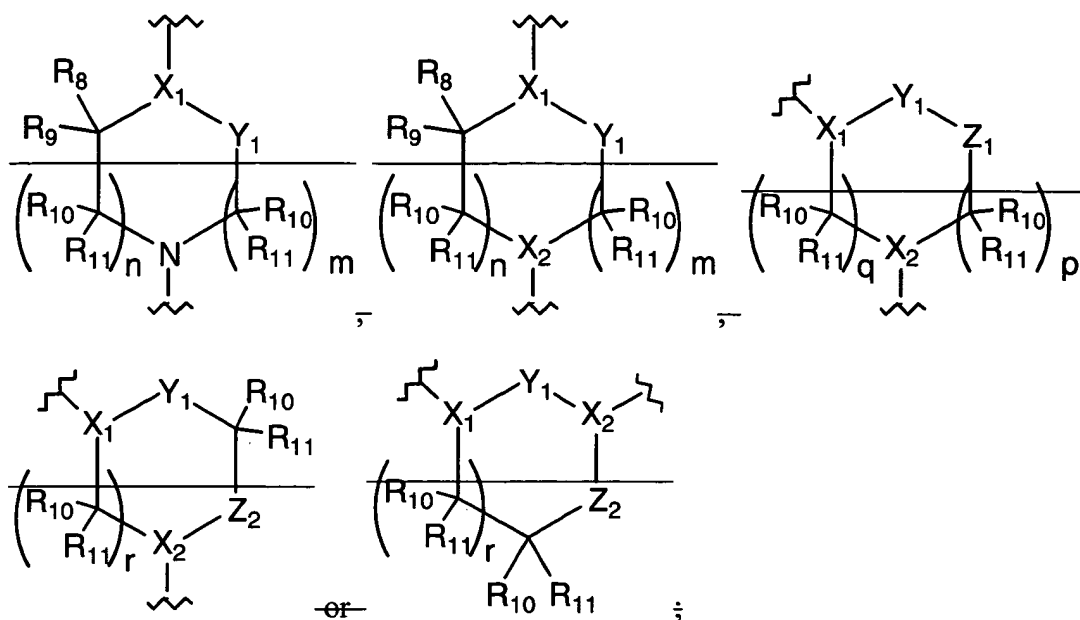
each  $W_2$ ,  $W_3$ ,  $W_4$  and  $W_5$  ~~are independently N or~~ is C- $R_4$ ; provided the total number of cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, -C(O)-O- $R_{19}$ , -C(O)- $R_{19}$ , -C(O)-NH- $R_{19}$ , -C(O)-N( $R_{19}$ )<sub>2</sub> and - $R_{19}$  radicals in  $W_2$ ,  $W_3$ ,  $W_4$  and  $W_5$  is 0-2;

each  $W_6$  ~~is independently N or C-H; provided that not more than two of  $W_2$ ,  $W_3$ ,  $W_4$ ,  $W_5$  and  $W_6$  represent N;~~ and

each  $R_4$  is independently a hydrogen, halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy, cyano, carboxy, -C(O)-O- $R_{19}$ , -C(O)- $R_{19}$ , -C(O)-NH- $R_{19}$ , -C(O)-N( $R_{19}$ )<sub>2</sub>, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of  $R_2$ ; or two adjacent  $R_4$  radicals taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 5-6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of  $R_2$ ;

$R_5$ ,  $R_6$  and  $R_7$  are each independently a hydrogen, halo, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, hydroxy or cyano radical; or  $R_5$  and  $R_6$  or  $R_6$  and  $R_7$  taken together with the carbon atoms to which they are attached represent a fused-phenyl or fused-heteroaryl of 6 ring members, wherein the phenyl and heteroaryl radicals are optionally substituted by 1-3 radicals of  $R_2$ ; or  $R_3$  and  $R_6$  taken together with the carbon atoms to which they are attached represent a fused-heteroaryl of 6 ring members optionally substituted by 1-3 radicals of  $R_2$ ;

A represents a radical of formula



wherein  $X_1$  is N or C-H;

$X_2$  is C-H, C-alkyl, a spirocycloalkyl or spiroheterocyclyl radical; wherein the spirocycloalkyl and spiroheterocyclyl radicals are optionally substituted by an oxo or thiooxo radical and 1-2 radicals of alkyl, haloalkyl, hydroxy, alkoxy or haloalkoxy;

$Y_1$  is  $C(O)$ ,  $C(S)$ ,  $S(O)$  or  $S(O)_2$ ;

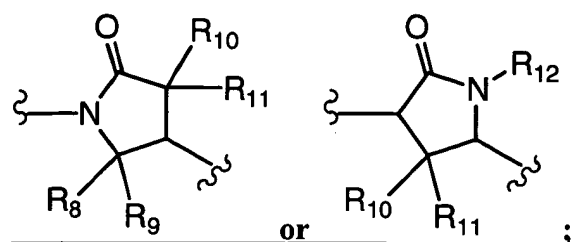
$Z_1$  is O or N- $R_{12}$ ;

$Z_2$  is O, S or N- $R_{12}$ ;

n and m are each independently 0, 1 or 2, provided  $n + m = 1, 2, 3$  or 4;

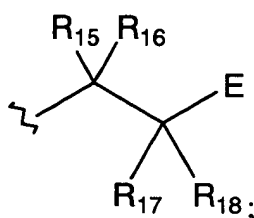
p and q are each independently 0, 1 or 2, provided  $p + q = 1, 2$  or 3;

r is 1 or 2;



$R_8$ ,  $R_9$ ,  $R_{10}$ ,  $R_{11}$  and  $R_{12}$  are each independently a hydrogen or alkyl radical; or  $-CR_8R_9-$  represents a  $-C(O)-$ ;

B represents a radical of formula



wherein (a)  $R_{15}$  is a hydrogen or alkyl radical; and  $R_{17}$  is (1) an aryl, heteroaryl,  $-NH-C(O)-R_{19}$ ,  $-C(O)-NH-R_{19}$ ,  $-NH-C(O)-NH-R_{19}$ ,  $-O-C(O)-NH-R_{19}$ ,  $-NH-C(O)-O-R_{19}$ ,  $-S(O)_2-R_{19}$ ,  $-NH-S(O)_2-R_{19}$ ,  $-S(O)_2-NH-R_{19}$  or  $-NH-S(O)_2-NH-R_{19}$  radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl,  $-NH-C(O)-R_{19}$ ,  $-C(O)-NH-R_{19}$ ,  $-NH-C(O)-NH-R_{19}$ ,  $-O-C(O)-NH-R_{19}$ ,  $-NH-C(O)-O-R_{19}$ ,  $-S(O)_2-R_{19}$ ,  $-NH-S(O)_2-R_{19}$ ,  $-S(O)_2-NH-R_{19}$  or  $-NH-S(O)_2-NH-R_{19}$ ; wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of  $R_2$ ; or

(b)  $R_{17}$  is a hydrogen or alkyl radical; and  $R_{15}$  is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl,  $-NH-C(O)-R_{19}$ ,  $-C(O)-NH-R_{19}$ ,  $-NH-C(O)-NH-R_{19}$ ,  $-O-C(O)-NH-R_{19}$ ,  $-NH-C(O)-O-R_{19}$ ,  $-S(O)_2-R_{19}$ ,  $-NH-S(O)_2-R_{19}$ ,  $-S(O)_2-NH-R_{19}$  or  $-NH-S(O)_2-NH-R_{19}$  radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl,  $-NH-C(O)-R_{19}$ ,  $-C(O)-NH-R_{19}$ ,  $-NH-C(O)-NH-R_{19}$ ,  $-O-C(O)-NH-R_{19}$ ,  $-NH-C(O)-O-R_{19}$ ,  $-S(O)_2-R_{19}$ ,  $-NH-S(O)_2-R_{19}$ ,  $-S(O)_2-NH-R_{19}$  or  $-NH-S(O)_2-NH-R_{19}$  radical; wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of  $R_2$ ;

provided that when a nitrogen atom is attached to the carbon atom to which  $R_{15}$  is attached, then  $R_{15}$  is (1) an aryl, heteroaryl, cycloalkyl, heterocyclyl or  $-C(O)-NH-R_{19}$  radical, or (2) an alkyl radical substituted by a radical of aryl, heteroaryl, cycloalkyl, heterocyclyl,  $-NH-C(O)-R_{19}$ , -



$C(O)-NH-R_{19}$ ,  $-NH-C(O)-NH-R_{19}$ ,  $-O-C(O)-NH-R_{19}$ ,  $-NH-C(O)-O-R_{19}$ ,  $-S(O)_2-R_{19}$ ,  $-NH-S(O)_2-R_{19}$ ,  $-S(O)_2-NH-R_{19}$  or  $-NH-S(O)_2-NH-R_{19}$ ;

wherein  $R_{19}$  is a alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, aryl-alkyl, heteroaryl, heteroaryl-alkyl, heterocyclyl or heterocyclyl-alkyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of  $R_2$ ;

$R_{16}$  and  $R_{18}$  are each independently a hydrogen or alkyl radical; and

E is a radical of carboxy, amido, tetrazolyl,  $-C(O)-O-R_{20}$ ,  $-C(O)-NH-R_{20}$ ,  $-C(O)-NH-S(O)-R_{20}$ ,  $-C(O)-NH-S(O)_2-R_{20}$  or  $-C(O)-NH-C(O)-R_{20}$ ;

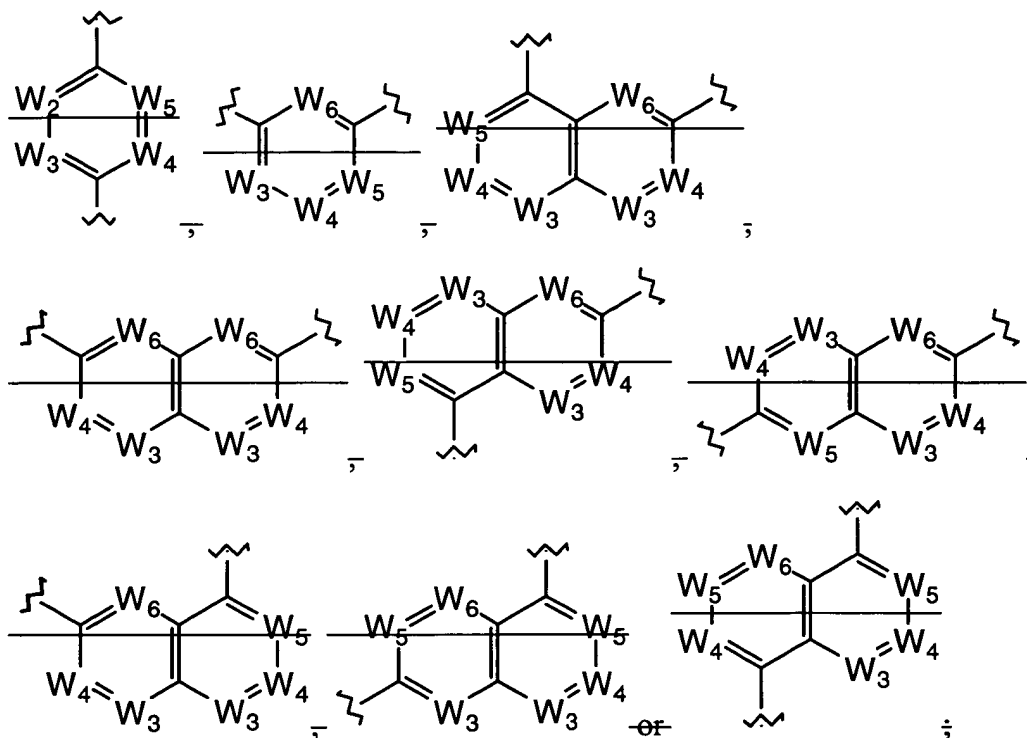
wherein  $R_{20}$  is an alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl radical or an alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of  $R_2$ ; and

provided that when U represents amidino, guanidino,  $-C(Q)-NH-R_1$  or  $-NH-C(Q)-NH-R_1$  radical, wherein Q represents NH, N-CN or N-alkyl, then at least one of g, h or j is 1.

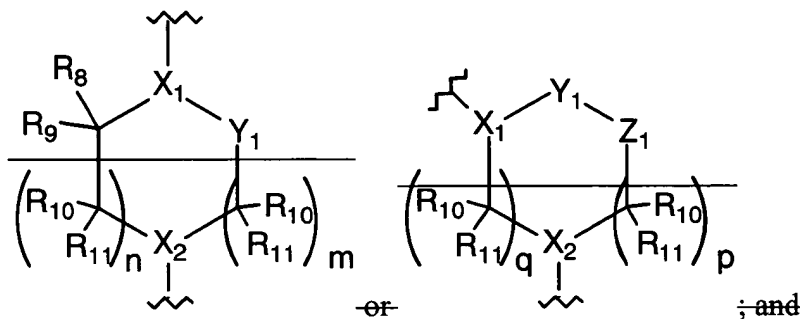
~~3. (Delete) The compound of Claim 2 or a pharmaceutically acceptable salt thereof, wherein~~

~~each Alk is independently a  $C_1-C_8$  alkyl radical;~~

~~V represents a radical of formula~~



A represents a radical of formula

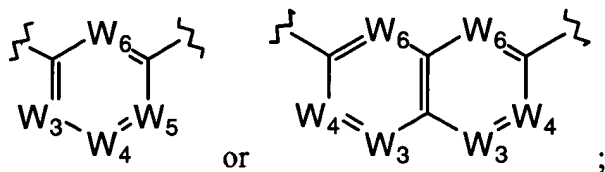


Y<sub>1</sub> is C(O) or C(S).

4. (Amended) The compound of Claim 2 or a pharmaceutically acceptable salt thereof, wherein

each Alk is independently a C<sub>1</sub>-C<sub>6</sub> alkyl radical;

V represents a radical of formula



$X_2$  is  $\text{C-H}$  or  $\text{C}$ -(methyl)-radical;

$Y_1$  is  $\text{C(O)}$ -; and

$R_8, R_9, R_{10}, R_{11}$  and  $R_{12}$  are each independently a hydrogen or methyl radical; or  $-\text{CR}_8\text{R}_9$ - represents a  $-\text{C(O)}-$ .

5. (Amended) The compound of Claim 4 or a pharmaceutically acceptable salt thereof, wherein

each Alk is independently a  $\text{C}_1$ - $\text{C}_4$  alkyl radical;

U represents amidino, guanidino,  $-(\text{G}-(\text{C}_1\text{-C}_8 \text{ alkyl}))_k\text{-NH-R}_1$ ,  $-(\text{G}-(\text{C}_1\text{-C}_8 \text{ alkyl}))_k\text{-NH-C(Q)-R}_1$ ,  $-(\text{G}-(\text{C}_1\text{-C}_8 \text{ alkyl}))_k\text{-C(Q)-N(R)-R}_1$ ,  $-(\text{G}-(\text{C}_1\text{-C}_8 \text{ alkyl}))_k\text{-NH-C(Q)-N(R)-R}_1$  or  $-(\text{G}-(\text{C}_1\text{-C}_8 \text{ alkyl}))_k\text{-NH-C(Q)-O-R}_1$  radical;

G represents a bond, O or NH;

Q represents O, S, NH, N-CN or N- $(\text{C}_1\text{-C}_4 \text{ alkyl})$ ;

R is a radical of hydrogen or  $\text{C}_1\text{-C}_4$  alkyl;

$R_1$  is a radical of  $\text{C}_1\text{-C}_6$  alkyl, halo( $\text{C}_1\text{-C}_6$  alkyl) of 1-5 halo radicals,  $\text{R}_{21}\text{R}_{22}\text{N}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $\text{R}_{21}\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$ ,  $\text{C}_3\text{-C}_8$  cycloalkyl,  $\text{C}_3\text{-C}_8$  cycloalkyl( $\text{C}_1\text{-C}_6 \text{ alkyl})$ , aryl, aryl( $\text{C}_1\text{-C}_6 \text{ alkyl})$ , heteroaryl of 5-10 ring members, heteroaryl( $\text{C}_1\text{-C}_6 \text{ alkyl})$  of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl( $\text{C}_1\text{-C}_6 \text{ alkyl})$  of 5-8 ring members, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of  $R_2$ ;

R<sub>21</sub> and R<sub>22</sub> are each independently a radical of hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl of 5-10 ring members or heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl) of 5-10 ring members, wherein the aryl and heteroaryl radicals are optionally substituted by 1-3 radicals of R<sub>2</sub>;

each R<sub>2</sub> is independently a halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, halo(C<sub>1</sub>-C<sub>2</sub> alkyl) of 1-5 halo radicals, halo(C<sub>1</sub>-C<sub>2</sub> alkoxy) of 1-5 halo radicals, hydroxy, carboxy, cyano, azido, amidino, guanidino, nitro, amino, C<sub>1</sub>-C<sub>4</sub> alkylamino or di(C<sub>1</sub>-C<sub>4</sub> alkyl)amino radical or two adjacent R<sub>2</sub> radicals on an aryl or heteroaryl radical represent a methylenedioxy, ethylenedioxy or propylenedioxy radical;

~~each W<sub>6</sub> is C-H;~~

each R<sub>4</sub> is independently a hydrogen, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, halo(C<sub>1</sub>-C<sub>2</sub> alkyl) of 1-5 halo radicals, halo(C<sub>1</sub>-C<sub>2</sub> alkoxy) of 1-5 halo radicals, hydroxy, cyano, carboxy, -C(O)-O-R<sub>19</sub>, -C(O)-R<sub>19</sub>, -C(O)-NH-R<sub>19</sub>, -C(O)-N(R<sub>19</sub>)<sub>2</sub>, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub> alkyl), aryl, aryl(C<sub>1</sub>-C<sub>4</sub> alkyl), heteroaryl of 5-10 ring members, heteroaryl(C<sub>1</sub>-C<sub>4</sub> alkyl) of 5-10 ring members, heterocyclyl of 5-8 ring members or heterocyclyl(C<sub>1</sub>-C<sub>4</sub> alkyl) of 5-8 ring members radical, wherein the cycloalkyl, aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R<sub>2</sub>; and

R<sub>20</sub> is a C<sub>1</sub>-C<sub>4</sub> alkyl, aryl or heteroaryl of 5-10 ring members or a C<sub>1</sub>-C<sub>4</sub> alkyl radical substituted by 1-3 radicals of halo, hydroxy, carboxy, amino, aryl, heteroaryl of 5-10 ring members or heterocyclyl of 5-8 ring members, wherein the aryl, heteroaryl and heterocyclyl radicals are optionally substituted by 1-3 radicals of R<sub>2</sub>.